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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,555	10/20/2000	Kenneth Kornman	MSA-009.01(20974-901)	7773

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/693,555	Applicant(s) KORNMAN ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 80-84* is/are pending in the application.

4a) Of the above claim(s) *17-32 and 42-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 80-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

1. Applicant's election with traverse of group I, claims 1-8 and 80-84 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the search for groups II and III would overlap with the search for group I and thereby would not require an undue search burden. This argument is not convincing because the search for group I is not co-extensive with the search of groups II and III. For example, a search for methods for determining an adverse pregnancy outcome does not lead one to all references teaching primers useful for amplifying the IL-1A (+4845) allele or IL-1B (-511) allele. Because primers which amplify these alleles may be used in numerous other types of methods (e.g., general genotyping methods, methods for determining susceptibility to periodontal disease, etc), one would clearly need to utilize different keywords to search these very distinct inventions. In addition, a search for methods for determining susceptibility to an adverse pregnancy outcome is distinct from a search of group III, which requires determining a TNF-A genotype (which is not required in the methods of group I) and determining any IL-1 genotype (which of a significantly broader and distinct scope than the methods of group I) and also requires identifying therapeutics which compensate for a LBW causative functional mutation (which is not required for the search of group I). Applicants further traverse the requirement to elect a single nucleic acid sequence. Applicants assert that there appears to be a problem which arises from "the Examiner's misapplication of the principle that different nucleic acids are different inventions. While the principle may reflect current case law with respect to compositions of matter type claims, Applicants assert that it is not intended to be applied to method claims, and particularly to method claims where the inventiveness does not

necessarily derive from the nucleic acid sequences alone". This argument is not convincing because the search of a nucleic acid sequence is the same whether that sequence is part of a method claim or part of a composition claim. The examiner believes that Applicants have misinterpreted the Office's policy regarding the restriction of nucleic acid sequences and requests that Applicants provide evidence of the case law which supports their allegation that the restriction requirement regarding nucleic acid sequences does not apply to method claims. With respect to Applicants comment regarding the inventiveness of methods not relying on the nucleic acids, if Applicants wish to state on the record that each of the claimed nucleic acid sequences of SEQ ID NO: 1-18 were well known in the art at the time the invention was made and provide references teaching each of these nucleic acid sequences, then the examiner will consider rejoining the nucleic acids of SEQ ID NO: 2-17 with the method of group I.

The requirement is still deemed proper and is therefore made FINAL.

2. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. In particular, Applicant is required to amend the specification to clearly state the relationship between the present application and application PCT/US99/08794. The priority data should clarify whether the instant application is a continuation-in-part or continuation of PCT/US99/08794.

3. Claims 1-8 and 80-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining a pregnant woman's

predisposition to having a low birth weight baby comprising detecting the presence of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2 wherein the detection of IL-1A (+4845) allele 2 and IL-1B (-511) allele 2 is indicative of a predisposition to having a low birth weight baby, does not reasonably provide enablement for methods which determine a predisposition to any adverse pregnancy outcome or methods which determine an adverse pregnancy outcome by detecting allele in linkage disequilibrium to of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2 or methods which detect any IL-1 allele 2 marker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-8 are drawn to a method for determining whether a subject is predisposed to having an adverse pregnancy outcome by detecting the presence of an of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2 or an allele in linkage disequilibrium with of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2. Claims 80-82 are drawn to methods for determining an increased susceptibility to an adverse pregnancy outcome comprising detecting any IL-1 allele 2 marker in a sample of fetal material. Accordingly, the claims include detecting, for example, IL-1A (-889), IL-1RN (VNTR), IL-1B (+3953), the 222/223 marker of IL-1A the gz5/gz6 marker of IL-1A etc. Claims 83-84 are drawn to methods for predicting an increased susceptibility to adverse pregnancy outcome comprising determining a the genetic polymorphism pattern of a subject for any IL-1A or IL-1B allele and comparing the subject's pattern to a control sample's IL-1A allele 2 and IL-1B (TaqI) allele 2 wherein "similarity" of the subject's pattern to the control's pattern

indicates susceptibility to an adverse pregnancy outcome. The specification (page 63) teaches that "White women showed a trend towards association between individuals carrying at least 1 copy of allele 2 at +4845 and -511 and low birth weight with an odds ratio of 2.83 (95% CI 0.196-40.97). A significant association was demonstrated in black women carrying at least 1 copy of allele 2 +4845 with an odds ratio of 4.8 (95% CI 1.155-19.951, P=0.033) with low birth weight. Furthermore, a significant association between low birth weight and genotype was demonstrated in black women carrying at least 1 copy of allele 2 at each locus of +4845 plus -511 with an odds ratio of 8.89 (95% CI 1.934-40.855, P=0.0068)." Accordingly, the specification teaches an association in black and white women between the presence of both the IL-1A (+4845) allele 2 and IL-1B (-511) allele 2 and low birth weight. In black women an association was also identified between the presence of the IL-1A (+4845) allele 2 and low birth weight. No association is disclosed between the IL-1B (-511) allele 2 alone and the occurrence of low birth weight or between the IL-1A (+4845) allele 2 and low birth weight in white woman. Accordingly, the specification has not enabled methods which determine susceptibility to low birth weight by detecting the presence of the IL-1A (+4845) allele 2 alone in the general population or by detecting the IL-1B (-511) allele 2. The specification does not teach an association between low birth weight and any other IL-1A, IL-B or IL-1RN alleles. Furthermore, the specification has not taught an association between low birth weight and any alleles in linkage disequilibrium with IL-1A (+4845) allele 2 or IL-1B (-511) allele 2. The art has not established a correlation between any alleles of IL-1 and the occurrence of adverse pregnancy

outcome which would allow for a general relationship to be established between the presence of an IL-1 gene cluster allele and any adverse pregnancy outcome. In particular, with respect to claims 83-84, the specification provides no information regarding the frequency of the IL-1B (Taq; +3953) allele or additional IL-1A allele (other than IL-1A (+4845) and the occurrence of LBW or adverse pregnancy response. While the specification postulates that alleles in linkage disequilibrium with the stated interleukin alleles could also be used to diagnose adverse pregnancy outcome, given the fact that other alleles are not in 100% linkage disequilibrium with the stated alleles and that stated alleles have variable frequencies of association with low birth weight, it is highly unpredictable as to whether alleles in linkage disequilibrium with of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2 or any other IL-1 allele would be sufficiently correlated with the occurrence of adverse pregnancy outcome or low birth weight. Further, while the specification suggests that IL-1 genotypes association with inflammation may be used to diagnose any disease that involves inflammation, Applicants have not provided sufficient evidence to establish that any level of inflammation or any inflammatory response in a pregnant women is correlated with adverse pregnancy outcome. Moreover, while the specification provides results regarding the frequency of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2 and the adverse pregnancy outcome of low birth weight, the specification has not taught an association between these alleles and any other type of adverse pregnancy outcome. Adverse pregnancy outcome includes many types of distinct conditions, such as preterm labor, premature rupture of membranes, still-birth, ectopic pregnancy, and abdominal pregnancy. Applicants have

not provided sufficient evidence to show that all adverse pregnancy outcomes are associated with inflammation and are correlated with the presence of any allele 2 IL-1 genotype. It would clearly require extensive experimentation for one of skill in the art to analyze all other types of adverse pregnancy outcomes to identify additional outcomes that are correlated with the presence of a particular IL-1 genotype, particularly given the high level of unpredictability in the art of establishing a correlation between an allele and the occurrence of a condition and given the lack of sufficient guidance provided by the specification. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has identified only 2 alleles in two IL-1 genes out of all possible IL-1 genes and has disclosed the use of only these alleles together as a means for diagnosing a predisposition to LBW. Thereby, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of IL-1 genes for additional alleles

which may be analyzed for their association with adverse pregnancy outcome. The specification has not provided any data regarding the frequency of additional IL-1 alleles (i.e., alleles other than IL-1A (+4845) allele 2 or IL-1B (-511) allele 2) in other types of conditions associated with adverse pregnancy outcome and has not established a universal correlation between IL-1 polymorphisms and all types of adverse pregnancy outcomes. Moreover, with respect to claim 8, the broadest reasonable interpretation of this claim indicates that the claim is inclusive of methods which identify novel alleles associated with low birth weight. While the specification is enabling for methods for detecting IL-1A (+4845) allele 2 and IL-1B (-511) allele 2 as indicative of an increase susceptibility to giving birth to a LBW baby, the specification is not enabling for methods which search for novel alleles that may be in linkage disequilibrium with IL-1A (+4845) allele 2 or IL-1B (-511) allele 2. To make and use an invention requires that the invention have a "real world" use. However, uses that require carrying out further research do not constitute a real world use. Thus, the specification has not adequately enabled methods which search for novel alleles associated with low birth weight. With respect to claims 80-82, the specification does not teach the frequency of any IL-1 alleles in a fetus and the occurrence of adverse pregnancy outcome. There is no information regarding the genotype of a fetus and how this effects the birth weight of the fetus or any other conditions associated with adverse pregnancy outcome. No association has been established between the fetal genotype and the maternal genotype which would allow one to conclude that if a maternal genotype is associated with LBW or adverse pregnancy outcome, then the same fetal genotype would also be associated

with LBW or adverse pregnancy outcome. Accordingly, in view of the lack of information in the specification as to how to reasonably identify other IL-1 alleles associated with low birth weight or adverse pregnancy outcome without undue experimentation and in view of the unpredictability in the art in correlating the presence of an allele with a specific condition, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

4. Claims 1-8 and 80-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 are indefinite and vague over the recitation of IL-1 (-511) because the claims do not set forth the complete identify of the stated allele. The claims should be amended to refer to "IL-1B (-511)".

Claims 1-8 are indefinite over the recitation of "the fetus" because this phrase lacks proper antecedent basis.

Claim 8 is indefinite for failing to recite a final process step which agrees back with the preamble. The claim is drawn to a method for identifying an allele associated with low birth weight. However, the final process step is one of identifying an allele in linkage disequilibrium with IL-1A (+4845) allele 2 or IL-1B (-511) allele 2. Accordingly, it is unclear as to whether the claim is intended to be limited to methods for identifying an allele associated with low birth

weight or methods of identifying an allele in linkage disequilibrium with IL-1A (+4845) allele 2 or IL-1B (-511) allele 2.

Claims 80-82 are indefinite over the recitation of "the individual's increased susceptibility to adverse pregnancy outcome" because the phrase "the individual's" lacks proper antecedent basis. The claims do not set forth the identify of the "individual" and t is unclear as to whether the individual is intended to be the same as the fetus. If the individual is distinct from the fetus, it is unclear as to what is intended to be the relationship between detecting an IL-1 marker in the fetus and determining an individuals susceptibility to an adverse pregnancy outcome.

Claims 83-84 are indefinite and vague over the recitation of "wherein the similarity of the genetic polymorphism pattern to the control sample indicates susceptibility" because it is unclear as to what is intended to be encompassed by "similar" patterns. For example, it is unclear as to whether patterns are considered to be similar only if they both contain an IL-1A allele 2 or IL-1B (-889) allele 2 or if they contain either an IL-1A allele 2 or IL-1B (Taq) allele 2 or if they would still be similar if they contained an IL-1A allele 1 and/or an IL-1B (-889) allele 1. The claims are further indefinite over the recitation of "IL-1A allele 2" because it is unclear as to whether this is intended to refer to a specific IL-1A allele (e.g., IL-1A (+4845)) or to any IL-1A allele.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper tames extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.d. 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Long*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.32 (c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 and 80-84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,268,142. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '142 are both inclusive of methods for diagnosing a disease by detecting the presence of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2. The instant claims are limited to methods for diagnosing adverse pregnancy outcome including preterm labor and low birth weight. The claims of '142 are inclusive of methods for diagnosing any disease

associated with a IL-1 inflammatory haplotype. As defined in '142, diseases associated with a IL-1 inflammatory haplotype are inclusive of preterm labor and low birth weight.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Duff et al (WO 98/54359; reference 'BB') discloses the concept of determining a patient's susceptibility to an inflammatory disorder by detecting the presence of an IL-1 allele, such as IL-1A (+4845) allele 2 or IL-1(-511) allele 2. It is noted that this reference, to which priority is claimed in U.S. Patent 6,268,142, does not specifically teach that the inflammatory disease may be low birth weight or adverse pregnancy outcome.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

March 21, 2002

CARLA J. MYERS
PRIMARY EXAMINER